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PATENT SPECIFICATION

716.647



Date of Application and filing Complete Specification: April 8, 1952.

No. 8974/52.

Application made in Canada on Nov. 15, 1951.

Complete Specification Published: Oct. 13, 1954.

Index at acceptance:—Class 2(3), C3C5, I(2: 4).

COMPLETE SPECIFICATION

Organic Thiol Derivatives of Metal-Containing Compounds

ERRATA

SPECIFICATION NO. 716,647

Page 4, line 77, for "monoamine" read "monoamide"

Page 4, line 112, for "coresponding" read "corresponding"

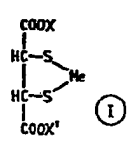
THE PATENT OFFICE,
17th March, 1961

DS 88425/1(2)/R. 153 200

or radicals. The invention also relates to compounds or derivatives of the before-mentioned type, which contain in the molecule, in addition to the radical or radicals of the 1,2-dimercaptosuccinic acid compound or the like, a radical or radicals of monomercapto or dimercapto derivatives of other organic compounds. The invention also includes the processes for preparing the above mentioned reaction products.

The new compounds are distinguished by their reduced toxicity and also by their solubility characteristics, in comparison with other compounds of the respective metals.

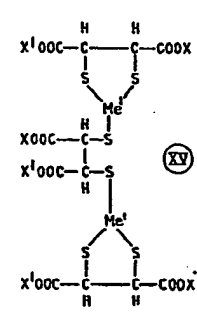
The present invention consists in the dimercapto derivative of a metal-containing compound, corresponding to the general formula:—



wherein —COOX and —COOX¹ may be equal or different and stand for:

- (a) an unsubstituted carboxyl group,
- (b) a carboxyl group substituted by an inorganic atom or group, by a radical of an

mercapto derivative of a metal-containing compound, corresponding to the general formula:



wherein —COOX and —COOX¹ may be equal or different and stand for an unsubstituted carboxyl group, for a carboxyl group substituted by an inorganic atom or group by a radical of an organic base, or by an alkyl radical, or for an amide radical, and =Me¹—stands for Au or Bi or Sb.

In the first-mentioned general formula, X and X¹ may stand for example for H, Li, K, Ca, Mg, —NH₂, radicals of methylamine, ethylamine, dimethylamine, diethylamine, diethanolamine, glucosamine, piperidine, amidines, such as pentamidine, radicals of

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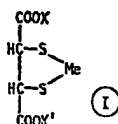
Organic Thiol Derivatives of Metal-Containing Compounds

I, ERNST ALBERT HERMANN FRIEDHEIM, of 333, West 52nd Street, New York, New York, United States of America, a Swiss citizen, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to organic dithiol derivatives of metal-containing compounds and has particular relation to reaction products of metal-containing compounds with dimercapto derivatives of 1,2-dimercapto-succinic acid or 1,2-dimercaptosuccinic acid compounds, in which one or both carboxyl groups may be substituted by suitable atoms or radicals. The invention also relates to compounds or derivatives of the before-mentioned type, which contain in the molecule, in addition to the radical or radicals of the 1,2-dimercaptosuccinic acid compound or the like, a radical or radicals of monomercapto or dimercapto derivatives of other organic compounds. The invention also includes the processes for preparing the above mentioned reaction products.

The new compounds are distinguished by their reduced toxicity and also by their solubility characteristics, in comparison with other compounds of the respective metals.

The present invention consists in the dimercapto derivative of a metal-containing compound, corresponding to the general formula:—



wherein —COOX and —COOX¹ may be equal or different and stand for:

- (a) an unsubstituted carboxyl group,
- (b) a carboxyl group substituted by an inorganic atom or group, by a radical of an

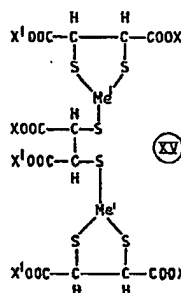
organic base, or by an alkyl or aryl radical, or

(c) an amide radical; and wherein Me stands either for:

(a) =Hg,

or for:
(b) a radical of Au, Bi or Sb of the formula =AuY, =BiY or =SbY, wherein Y stands for —OH or an inorganic acid radical, or a radical of an acid or for an —SR radical, in which R is an inorganic atom or group, or a residue or radical of an aliphatic or aromatic compound, or for an aliphatic or aromatic organic radical bound by a C-atom to the metal atom.

The invention further consists in the dimercapto derivative of a metal-containing compound, corresponding to the general formula:

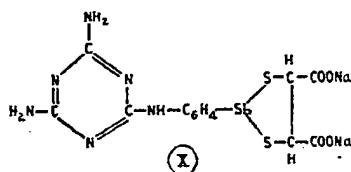
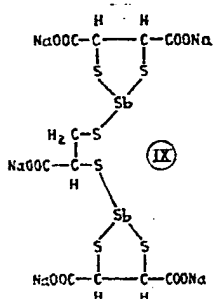
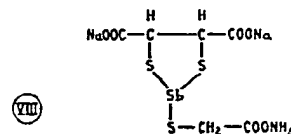
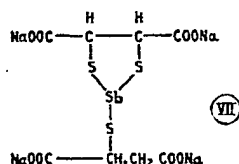
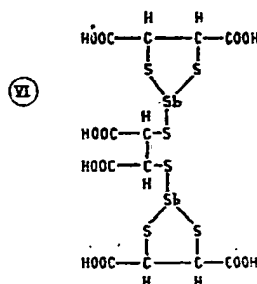
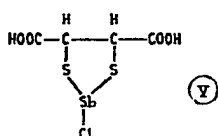
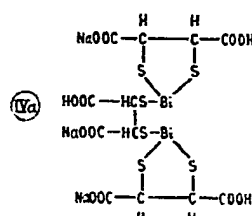
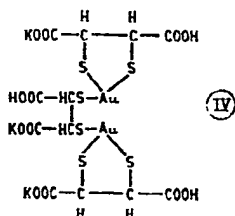
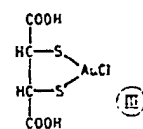
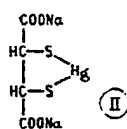


wherein —COOX and —COOX¹ may be equal or different and stand for an unsubstituted carboxyl group, for a carboxyl group substituted by an inorganic atom or group by a radical of an organic base, or by an alkyl radical, or for an amide radical, and =Me¹—stands for Au or Bi or Sb.

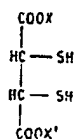
In the first-mentioned general formula, X and X¹ may stand for example for H, Li, K, Ca, Mg, —NH₂, radicals of methylamine, ethylamine, dimethylamine, diethylamine, diethanolamine, glucosamine, piperidine, amidines, such as pentamidine, radicals of

amides and substituted amides, methyl, ethyl, phenyl radicals. Examples of R are Na, $-\text{NH}_2$, radical of thioglycolic acid, i.e., $-\text{CH}_2\text{COOH}$ and its salts, and $-\text{C}_6\text{H}_5$.

- 5 Thus, compounds embodying the present invention have, for example, one of the following formulas:—



- 10 In order to prepare the reaction products embodying the present invention, compounds of metals, such as salts, complex compounds, oxides, hydroxides, or organometallic compounds, are reacted with a dimercapto compound of the formula
- 15



wherein $-\text{COOX}$ and $-\text{COOX}'$ have the meaning defined above in connection with formula I, in a liquid reaction medium. 1,2-dimercaptosuccinic acid is preferably used in the form of aqueous solutions of its salts. The latter can be formed from the acid and hydroxides, bicarbonates, carbonates of alkali metals, hydroxides of alkaline earth metals, ammonia, organic bases, such as methylamine, ethylamine, diethylamine, diethanolamine, piperidine and amidines, such as pentamidine. Monobasic and dibasic salts of

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1,2-dimercaptosuccinic acid can be used. The reaction can be carried out also in organic solvents. For example, HgCl_2 can be reacted in methanol with free 1,2-dimercaptosuccinic acid. The 1,2-dimercaptosuccinic acid derivatives embodying the present invention may be prepared in the form of free acids, acid salts and neutral salts.

The reaction products can be isolated from the reaction mixture by evaporation of the reaction liquid or by precipitation with suitable organic solvents or reagents.

EXAMPLE 1.

1 mol of freshly precipitated $\text{Sb}(\text{OH})_3$ is suspended in an aqueous solution of 1.5 mol of 1,2-dimercaptosuccinic acid and 3 mols of NaHCO_3 in 1 litre of water and agitated until the $\text{Sb}(\text{OH})_3$ is dissolved. After filtration and adjustment to the desired concentration, the solution can be used for therapeutic administration. The reaction product can be isolated by evaporation of the liquid reaction medium *in vacuo* or by precipitation with acetone, and can be purified by crystallization from water. The free acid derivative corresponding to the above formula (VI), can be isolated by precipitation with HCl from the reaction mixture. The acid K salt can be obtained by dissolving the free acid derivative in aqueous potassium acetate solution and precipitation with alcohol. $\text{Sb}(\text{OH})_3$ may be also reacted with free 1,2-dimercaptosuccinic acid by suspending $\text{Sb}(\text{OH})_3$ and the free acid in methanol. A soluble reaction product is formed which separates in crystalline form upon evaporation *in vacuo*. The mono—Na or mono—K salt can be obtained by addition of the corresponding alkali acetate to the methanol solution.

EXAMPLE 2.

In order to form a salt of antimony-1,2-dimercaptosuccinic acid of the formula $\text{C}_{12}\text{H}_{12}\text{O}_{12}\text{S}_6\text{Sb}_2$, 1 mol of tartar emetic is dissolved in an aqueous liquid prepared by dissolving 1.6 mol of 1,2-dimercaptosuccinic acid and 1.6 mol of Na_2CO_3 in 1 litre of water. The resulting solution is filtered in order to remove mechanical impurities as well as bacteria and is then suitable for therapeutic administration to human patients or animals. The free acid derivative and the acid alkali salt can be obtained in the same manner as in Example 1.

EXAMPLE 3.

1 mol of freshly precipitated $\text{Sb}(\text{OH})_3$ is dissolved under stirring in an aqueous solution of 3 mols of ammonium thioglycolate ($\text{HS}-\text{CH}_2-\text{COONH}_4$) and 1 mol of the disodium salt of 1,2-dimercaptosuccinic acid in 1 litre of water. The resulting solution is evaporated to dryness under reduced pressure and the solid residue is several times recrystallized from water. The resulting product corresponds to the above formula (VIII).

Products corresponding to the above for-

mulas (VII) and (IX) can be prepared in similar manner.

EXAMPLE 4.

1 mol of bismuth ammonium citrate is dissolved in 1 litre of water and to the solution 1.5 mols of the disodium salt of 1,2-dimercaptosuccinic acid, dissolved in water, are added. The resulting solution is filtered and adjusted to a $\text{pH}=7.0$ and is then suitable for therapeutic administration. The reaction product has the probable formula IVa denoted above.

EXAMPLE 5.

1 mol of freshly precipitated $\text{Bi}(\text{OH})_3$ is suspended in an aqueous solution of 1.5 mols of the disodium salt of 1,2-dimercaptosuccinic acid in 1 litre of water and the mixture is stirred until the $\text{Bi}(\text{OH})_3$ is dissolved. Further treatment of the solution thus obtained substantially corresponds to that described in Example 1. The reaction product thus obtained is identical with that formed in Example 4.

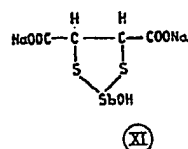
EXAMPLE 6.

To an aqueous solution of 1 mol of HgCl_2 in 1 litre of water, an aqueous solution of 1 mol of the disodium salt of 1,2-dimercaptosuccinic acid and 2 mols of sodium bicarbonate are added. After filtration, the reaction product can be isolated by evaporation under reduced pressure and purified by crystallization. The reaction product has the probable formula II denoted above.

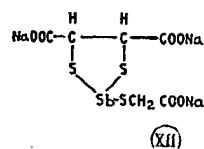
A similar reaction product representing the free acid derivative, is obtained by precipitation of the above described dissolved reaction product with HCl or by reacting HgCl_2 dissolved in methanol, with free 1,2-dimercaptosuccinic acid.

EXAMPLE 7.

1 mol of freshly precipitated $\text{Sb}(\text{OH})_3$ is dissolved under stirring in an aqueous solution of 1 mol of the disodium salt of 1,2-dimercaptosuccinic acid in 1 litre of water. The reaction product formed corresponds to the formula



By adding to the solution of this product 1 mol of the sodium salt of thioglycolic acid, dissolved in water, a compound corresponding to the following formula is formed:

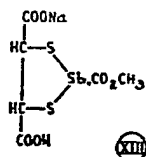


EXAMPLE 8.

0.1 mol of sodium *p*-melaminyl-phenylstibonate is stirred in an oxygen-free atmosphere into a solution of 0.25 mols of the disodium salt of 1,2-dimercaptosuccinic acid in 500 ccm. of water. The reaction mixture is kept at 40° C., and stirring is continued until a substantially clear solution is obtained. The latter is filtered and evaporated under reduced pressure to dryness. The residue contains the product corresponding to formula (X). It is purified by acid precipitation from its aqueous alkaline solution.

EXAMPLE 9.

1 part by weight of antimony acetate of the formula $\text{Sb}(\text{CO}_2\text{CH}_3)_3$ is stirred into a hot solution of 1 part by weight of 1,2-dimercaptosuccinic acid in 25 parts of methanol. The resulting solution is filtered and saturated with anhydrous sodium acetate. A white precipitate is formed which is filtered off and dried *in vacuo*. The product has the probable formula



The compound is very soluble in water to give a colorless clear solution of a pH of 4—5. Furthermore, dimercapto derivatives of other organometallic compounds can be prepared by reacting with 1,2-dimercaptosuccinic acid or its salts, substantially in the manner described in the above examples, for example monosodium *p*-aminophenylstibonate and monosodium acetylaminophenylstibonate. In the treatment of Sb compounds containing a pentavalent metal atom connected to a C atom, I prefer to react such compounds first with an organic monothiol, for example ammonium thioglycolate and subsequently react the monothiol derivative with the 1,2-dimercaptosuccinic acid compound. The pentavalent metal compounds may also be reduced to the corresponding trivalent derivatives and condensed with dimercaptosuccinic acid in one operation, by reaction with at least 2.5 mols of dimercaptosuccinic acid.

EXAMPLE 10.

$\text{AuCl}_3 \cdot \text{HCl}$ and 1,2-dimercaptosuccinic acid are reacted in methanol in the molecular proportion of 2:3. For example, 1 mol of the gold compound and 1.5 mol of said dimercapto acid are reacted in 800 ccm of methanol. The solution thus obtained is evaporated to dryness, under vacuum, and the dry residue is dissolved in aqueous sodium acetate solution. By precipitation of the filtered solution with alcohol, a compound corresponding to formula (IV) is obtained.

EXAMPLE 11.

1 mol of $\text{Au}(\text{NH}_2)_2\text{Cl}$ (diamido aurichloride) is suspended in an aqueous solution of 1.5 mol of the disodium salt of 1,2-dimercaptosuccinic acid in 1 litre of water and the reaction mixture is stirred until the gold compound is dissolved. The reaction product corresponds to the formula $\text{C}_{12}\text{H}_{10}\text{O}_{12}\text{S}_4\text{Au}_2\text{Na}_2 \cdot 2\text{H}_2\text{O}$.

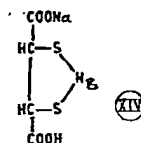
EXAMPLE 12.

1 mol of freshly precipitated $\text{Sb}(\text{OH})_3$ and 1.5 mol of the monomethyl ester of 1,2-dimercaptosuccinic acid are suspended in one litre of water and reacted under stirring in an aqueous solution of 3 mols of NaHCO_3 until a clear solution is formed. The further treatment is similar to that described in Example 1.

Furthermore, $1\frac{1}{2}$ mol of the dimethylester or of the monoamine of 1,2-dimercaptosuccinic acid can be reacted with 1 mol of $\text{Sb}(\text{OH})_3$ in methanol in the manner described in Example 1.

The 1,2-dimercaptosuccinic acid can be prepared by reacting acetylene-dicarboxylic acid, in the form of its salts with inorganic or organic bases, with 2 molecules of thioacetic acid (CH_3COSH) to form the corresponding dithioacetyl esters which can be readily hydrolyzed to the corresponding dithiols. For example, 10 grams of the dipotassium salt of acetylene dicarboxylic acid are dissolved in 100 ml. of water, and 7.5 ml. of thioacetic acid are gradually added under cooling and stirring, and stirring is continued first in an ice bath for about 3 hours and then at 15° to 25° C. for further 3 hours. The reaction mixture is acidified with HCl and heated to about 90° C. The 1,2-dimercaptosuccinic acid separates in the form of white crystals having a melting point of 192°—193° C.

I have found that the compounds embodying the present invention are of surprisingly low toxicity. For example, the antimony compound of the 1,2-dimercaptosuccinic acid is tolerated by mice in a dose of 2.5 g/kg. Furthermore, a water-soluble compound of the formula



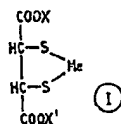
formed by reacting equimolecular quantities of 1,2-dimercaptosuccinic acid and mercury dichloride in methanol solution, and addition of an excess of sodium acetate, is tolerated by mice in an i.p. dose corresponding to 0.06 g/kg. of mercury, while mercury bichloride is toxic in a dose corresponding to 0.002 g/kg. of mercury, under equal conditions. The

compounds of the above mentioned metals and 1,2-dimercaptosuccinic acid compounds, can be administered in therapeutic applications, by themselves or in the form of a mixture with organic vicinal dithiols, particularly 1,2-dimercaptosuccinic acid or its derivatives.

In carrying out the process of the invention, the ratio between the dimercaptosuccinic acid compound and the metal-containing compound can be varied. For example, one mole or more of the 1,2-dimercaptosuccinic acid compound can be used for 2 valencies of the metal. Furthermore, if the metal used has more than 2 valencies, the metal-containing compound can be reacted with 1 mol of 1,2-dimercaptosuccinic acid and with an additional amount of an organic mono-, di- or polymercapto compound for 1 atom of the metal, in order to bind all valencies of the metal to mercapto sulfur atoms.

What I claim is:—

1. As a new compound, the dimercapto derivative of a metal-containing compound, corresponding to the general formula:



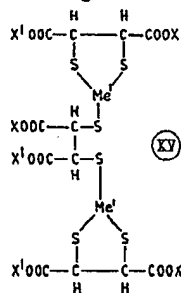
wherein —COOX and —COOX' may be equal or different and stand for:

(a) an unsubstituted carboxyl group,
(b) a carboxyl group substituted by an inorganic atom or group, by a radical of an organic base, or by an alkyl or aryl radical, or

(c) an amide radical;
and wherein Me stands either for:

(a) =Hg,
or for:
(b) a radical of Au, Bi or Sb of the formula =AuY, =BiY or =SbY, wherein Y stands for —OH or for an inorganic acid radical, or a radical of an organic acid, or for an —SR radical, in which R is an inorganic atom or group, or a residue or radical of an aliphatic or aromatic compound, or for an aliphatic or aromatic radical bound by a C-atom to the metal atom.

2. As a new compound, the dimercapto derivative of a metal-containing compound, corresponding to the general formula:



wherein —COOX and —COOX' may be equal or different and stand for an unsubstituted carboxyl group, for a carboxyl group substituted by an inorganic atom or group, by a radical of an organic base, or by an alkyl radical, or for an amide radical, and =Me'— stands for Au, or Bi or Sb.

3. A new dimercapto derivative as claimed in claim 1, in which =Me stands for =Hg.

4. A new dimercapto derivative as claimed in claim 1, in which =Me stands for =AuY.

5. A new dimercapto derivative as claimed in claim 2, in which =Me'— stands for =Au—.

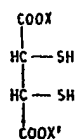
6. A new dimercapto derivative as claimed in claim 1, in which =Me stands for =SbY.

7. A new dimercapto derivative as claimed in claim 2, in which =Me'— stands for =Sb—.

8. A new dimercapto derivative as claimed in claim 1, in which =Me stands for =BiY.

9. A new dimercapto derivative as claimed in claim 2, in which =Me'—stands for =Bi—.

10. A process for producing dimercapto derivatives of compounds containing one of the metals Au, Bi, Hg or Sb, comprising reacting a compound containing one of said metals, with a 1,2-dimercaptosuccinic acid compound of the formula



wherein —COOX and —COOX' have the meaning defined in claim 1, in the presence of an organic or aqueous liquid and, if desired, separating the reaction product by evaporation or precipitation.

11. A process as claimed in claim 10, in which more than one mol of the 1,2-dimercaptosuccinic acid compound is used for 2 valencies of the metal.

12. A process as claimed in claim 10, in which the metal-containing compound and the 1,2-dimercaptosuccinic acid compound are reacted in a ratio, at which one mercapto group (—SH), i.e., $\frac{1}{2}$ mol of the 1,2-dimercaptosuccinic acid, corresponds to each valency of the metal.

13. A process as claimed in claim 10, in which the metal has more than 2 valencies and the metal-containing compound is reacted with 1 mol of the 1,2-dimercaptosuccinic acid and with an additional amount of an organic mono-, di- or polymercapto compound for 1 atom of the metal, in order to bind all valencies of the metal to mercapto-sulfur atoms.

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